DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 11 2010

J. Michael Nicholas, Ph.D.
Senior Director
Strategic Regulatory Affairs
Teva Neuroscience, Inc.
901 E. 104th Street, Suite 900
Kansas City, MO 64131

Re: Docket No. FDA-2009-P-0555

Dear Dr. Nicholas:

This letter responds to your citizen petition received on November 13, 2009 (Petition), and submitted on behalf of Teva Pharmaceutical Industries Ltd. (Teva). In the Petition, you request that the Food and Drug Administration (FDA or Agency) not approve any abbreviated new drug application (ANDA) for a purported generic version of Copaxone (glatiramer acetate) injection unless and until:

(1) Copaxone has been fully characterized (i.e., every polypeptide sequence of the drug has been identified and quantified, and its structure fully elucidated) and the ANDA applicant has proven that its product contains exactly the same polypeptide sequences, in the same amounts and with the same structures, as Copaxone; or

(2) All polypeptide sequences that contribute to the therapeutic effects of Copaxone have been identified, and the ANDA applicant has proven that:

- Its product contains exactly the same clinically relevant polypeptide sequences, in the same amounts and with the same structures, as Copaxone; and

- Any differences between the non-clinically active polypeptides in its product and those in Copaxone do not undermine the clinically active polypeptides' safety, efficacy, toxicology, and immunology profiles.

You state that you are requesting this action because you believe it is not currently possible for the sponsor of an ANDA to meet the conditions you have identified to show that its drug has the "same active ingredient" because neither Copaxone nor any significant subset of its polypeptides has been fully characterized, and because it is unknown which of Copaxone's potentially

FDA-2009-P-0555

PDN

millions of protein-like polypeptides are clinically active and responsible for its therapeutic effects in reducing the frequency of relapses in patients with relapsing-remitting multiple sclerosis (RRMS).[1]

We have carefully considered the Petition and comments filed in the docket. For the reasons stated below, the Petition is denied.

I. BACKGROUND

A. Copaxone

Teva Pharmaceuticals USA is the NDA holder for Copaxone (glatiramer acetate) injection, 20 milligrams (mg)/milliliter (mL) and 20 mg/vial (NDA 20-622). NDA 20-622 was approved on December 20, 1996. Glatiramer acetate is a heterogeneous mixture of synthetic polypeptides constructed from four naturally occurring amino acids — L-glutamic acid, L-alanine, L-tyrosine, and L-lysine (Petition at 10). The average molar fraction of these four amino acids is 0.141, 0.427, 0.095, and 0.338, respectively, and the average molecular weights of the polypeptides comprising glatiramer acetate range from 5000 to 9000 Daltons (Petition at 10). The polypeptides that compose glatiramer acetate appear to range from approximately 20 to 200 amino acids in length, with an average polypeptide length of about 60 amino acids (Petition at 10). The amino acid sequences and polypeptide chain lengths in Copaxone are not entirely random, but rather depend upon the reaction chemistry for the component amino acid monomers (Petition at 10). The resultant drug product is, therefore, a mixture of peptide copolymers with defined composition, and physicochemical properties that according to Teva are conserved from batch to batch in Teva's manufacturing process (Petition at 10). Copaxone is prepared using a well-controlled polymerization process, followed by a well-controlled cleavage (depolymerization) reaction (Petition at 10).

Copaxone is indicated for the reduction of the frequency in relapses in patients with RRMS, including patients who have experienced a first clinical episode and have magnetic resonance imaging (MRI) features consistent with multiple sclerosis.

B. Section 505(q) of the Act

The Petition is subject to section 914 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), which amended section 505 of the Food Drug and Cosmetics Act (FDCA or the Act) (21 U.S.C. 355) by adding new subsection (q). Section 505(q) of the Act applies to certain citizen petitions and petitions for stay of Agency action that request that FDA take any form of

[1] In an earlier citizen petition, FDA-2008-P-0529, submitted on September 26, 2008 you asked that we *not approve or accept for filing any ANDA or 505(b)(2) application* for a purported generic version or other pharmaceutical alternative to Copaxone unless the applicant satisfied certain conditions similar in many respects to those set forth in the current petition. We denied your earlier petition on March 25, 2009, without comment on the actions requested because we had not yet made a final decision on whether to approve or not approve any such applications.

action relating to a pending application submitted under section 505(b)(2) or (j) of the Act (21 U.S.C. 355(b)(2) or (j)) and governs the manner in which these petitions are treated. Among other things, section 505(q)(1)(F) of the Act governs the time frame for final Agency action on a petition subject to section 505(q). Under this provision, FDA must take final Agency action on a petition not later than 180 days after the date on which the petition is submitted. The 180-day period is not to be extended for any reason.

C. Statutory and Regulatory Provisions Regarding Active Ingredient Sameness for ANDA Approval

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the Act, which established the ANDA approval process. To obtain approval, an ANDA applicant is not required to submit clinical studies to establish the safety and effectiveness of the drug product. Instead, an ANDA applicant relies on the Agency's previous finding that the reference listed drug (RLD) is safe and effective. To rely on FDA's previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that the generic drug product is bioequivalent to the RLD (section 505(j)(2)(A)(iv) of the Act).[2] In addition, an ANDA must contain sufficient information to show that the generic drug product has the same active ingredient(s), previously approved conditions of use, route of administration, dosage form, strength, and (with certain exceptions) labeling as the RLD (sections 505(j)(2)(A) and (j)(4) of the Act). The Agency must approve the ANDA unless, among other things, the ANDA applicant has provided insufficient evidence of the foregoing, or if the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity (section 505(j)(4) of the Act).

The premise underlying the Hatch-Waxman Amendments is that drug products that are (1) approved as safe and effective, (2) pharmaceutically equivalent,[3] (3) bioequivalent, (4) adequately labeled, and (5) manufactured in compliance with Current Good Manufacturing Practice regulations are therapeutically equivalent and can be substituted for each other with the "full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed [RLD] product."[4]

---

[2] Under the Act, "[a] drug shall be considered to be bioequivalent to a listed drug if . . . the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses." See section 505(j)(8)(B)(i); see also implementing regulations at 21 CFR part 320.

[3] See 21 CFR 320.1(c) (pharmaceutical equivalents means, in part, drug products in identical dosage forms that contain identical amounts of the identical active ingredient and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency) and FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the Orange Book), 30th Ed., at vi-vii (available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf (last accessed May 11, 2010)).

[4] Orange Book at iv.

Section 505(j)(2)(A)(ii)(I) of the Act states that, for a single active ingredient drug product, an ANDA must contain information to show that the active ingredient[5] of the generic drug product is the "same as" that of the listed drug. Under section 505(j)(4) of the Act, FDA must approve an ANDA referencing a listed drug that has only one active ingredient unless the ANDA contains insufficient information to show that the active ingredient is the same as that of the listed drug (section 505(j)(4)(C)(i) of the Act), or otherwise does not meet the requirements for approval.

These statutory provisions do not, however, describe the type or amount of information that an ANDA applicant must submit to demonstrate that the active ingredient in the generic drug product is the same as the active ingredient in the RLD, nor do these provisions describe the type or amount of information on which FDA may rely in determining whether the ANDA applicant has provided sufficient information to show that the active ingredient is the same. Accordingly, Congress recognized that FDA must have broad discretion with respect to the information the Agency may consider in making a finding on the "sameness" of an active ingredient.[6]

Parallel FDA regulations implementing these statutory provisions (i.e., sections 505(j)(2)(A)(ii) and (j)(4)(C)) can be found at 21 CFR 314.94(a)(5)(i) and 314.127(a)(3). FDA regulations also provide that an ANDA is suitable for consideration and approval if the generic drug product is the same as the RLD (21 CFR 314.92(a)(1)). Specifically, § 314.92(a)(1) states that the term "same as" means, among other things, "identical in active ingredient(s)." In the preamble to the final rule implementing title I of the Hatch-Waxman Amendments, FDA specifically rejected the suggestion that the Agency adopt a requirement that active ingredients "exhibit the same physical and chemical characteristics, that no additional residues or impurities can result from the different manufacture or synthesis process; and that the stereochemistry characteristics and solid state forms of the drug have not been altered."[7] Instead, FDA adopted a more flexible approach, stating that it would "consider an active ingredient [in a generic drug product] to be the same as that of the reference listed drug if it meets the same standards for identity."[8] FDA further stated that, in most cases, the standards for identity are described in the USP, although the Agency might prescribe "additional standards that are material to the ingredient's sameness."[9]

Thus, as FDA's regulations and preamble reflect, FDA has broad discretion in determining whether an ANDA applicant has submitted sufficient information upon which the Agency can

---

[5] FDA regulations (at 21 CFR 210.3(b)(7)) provide that "*[a]ctive ingredient* means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." FDA regulations (at 21 CFR 314.3(b)) also provide that "*drug substance* means an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use[d] in the synthesis of such ingredient."

[6] See generally *Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998).

[7] See 57 FR 17950 at 17958-59 (April 28, 1992).

[8] Id. at 17959.

[9] Id.

reasonably conclude that the generic drug product's active ingredient is the "same as" that of the RLD. This flexible, science-based approach to determining active ingredient sameness has been sustained by the courts. Specifically, the U.S. Court of Appeals for the District of Columbia's decision in *Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998) (*Serono*), considered the ANDA approval requirements regarding active ingredients described in the Act and FDA regulations, and supported FDA's approach to determining the sameness of an active ingredient.[10]

The D.C. Circuit upheld as reasonable the Agency's interpretation of the "sameness" statutory requirement, as well as the Agency's interpretation of the word "identical" in 21 CFR 314.92(a)(1).[11] The court concluded that the statute does not unambiguously require the term "same as" to be defined as "complete chemical identity," noting that the statute says nothing at all about the type of information an applicant must submit to demonstrate "sameness" nor about the type of information upon which the FDA may rely.[12] The court characterized the sameness provision as a "broad grant of discretion" to the Agency with respect to the information it may consider and noted that the phrase "must be read in the context of the kind of drug at issue."[13]

FDA will continue its practice of taking into account the "kind of drug at issue" when making a determination of sameness. Any such determination would be based on current scientific data and information, the Agency's knowledge of the drug, its scientific experience and expertise, and the nature and extent of the data and information provided by an ANDA sponsor to support approval of its generic drug.

II. SPECIFIC ASSERTIONS IN THE PETITION

In the Petition, you assert that, because the active ingredient in Copaxone has not been fully characterized, it is not possible for an ANDA sponsor to demonstrate that its glatiramer acetate injection drug product referencing Copaxone contains the same active ingredient as Copaxone under section 505(j) of the Act, and 21 CFR §§ 314.92 and 314.127 (Petition at 4, 17-19, 20), and that even if the active ingredient were more fully characterized it cannot be determined which of the numerous polypeptides that comprise the active ingredient contribute to the clinical efficacy of Copaxone. Your reasons are as follows.

---

[10] *Serono* involved a legal challenge to our approval of a generic version of Pergonal, a menotropin product used to treat infertility. This product contains two active ingredients: follicle-stimulating hormone (FSH) and luteinizing hormone (LH). As the court noted, we concluded that to be the same, the generic drug product's active ingredients and Pergonal's active ingredients were expected to have the same primary structure, potency, and degree of batch-to-batch uniformity. One of the active ingredients included natural variations known as microheterogeneity. We maintained that an isoform variation in the active ingredient of the generic drug product did not preclude a finding of active ingredient "sameness" for purposes of ANDA approval. We noted in documents cited by the court that "complete chemical identification of all the carbohydrate variants in a protein product often is not possible or feasible." Id. at 1318. We stated "[i]ndeed, it usually is not even possible to 'assure by chemical analysis that different batches' of the same product 'are identical at the level of the carbohydrate side chains' – including different batches of Pergonal itself." Id. We stated that any isoform variations between the generic product and the RLD "appear not to be clinically significant for the product's intended uses." Id. at 1318.

[11] Id. at 1321.

[12] Id. at 1319.

[13] Id.

A. Copaxone's Complexity

You assert that to date (the date the Petition was filed) you have been unable to fully characterize the polypeptides in glatiramer acetate due to their number, structural complexity, and the current limitations of analytical technologies (Petition at 3). You base this assertion on your own research over the last 20 years, which you state has led to only a partial characterization of the drug, and on the views of pioneering academic researchers responsible for developing state-of-the-art techniques in analytical chemistry (Petition at 3).

You assert that while you have been able to glean a partial picture of glatiramer acetate by conducting certain tests[14] to measure the drug's "bulk" properties (i.e., the general properties of the entire glatiramer acetate mixture across batches of Copaxone), such tests do not provide information on the specific amino acid sequences that form glatiramer acetate's many protein-like polypeptides, the primary and higher order structures of these polypeptides, or the frequency with which they occur in the mixture (Petition at 11-13, 22-23). You thus assert that while the aforementioned tests help ensure that your controlled manufacturing process generates a consistent product and can be used to identify differences between batches of Copaxone, they cannot demonstrate that the clinically relevant polypeptide sequences in two glatiramoid products manufactured by different processes are identical (Petition at 11).

Moreover, you also assert that random polymerization techniques cannot be used to "reverse engineer" an identical product ((Petition at 10). Specifically, you state that using random polymerization to form a copolymer composed of polypeptides that average 60 units in length and are based on four constituent monomers (amino acids) would generate an astronomical number of potential sequences, and that it has been estimated that any of $>10^{29}$ different potential polypeptide sequences could be found in Copaxone (Petition at 10).

B. Unknown Components of Copaxone Responsible for the Drug's Favorable Clinical Safety and Efficacy Profile

You assert that it remains unknown which of Copaxone's potentially millions of protein-like polypeptides are clinically active and responsible for its therapeutic effects in treating RRMS (Petition at 3-4). You assert that the tests that measure the bulk properties of glatiramer acetate (see Footnote 14) do not provide information on which polypeptides provide or contribute to the product's proven therapeutic or clinical effects (Petition at 11-13, 22-23). You also assert that because the bulk properties of certain subsets (or fractions) of glatiramer acetate separated from the rest of the drug mixture using advanced chromatographic techniques vary significantly from each other (as well as from the unfractionated glatiramer acetate as a whole) you believe that glatiramer acetate's unique (if incompletely characterized) mixture of protein-like polypeptides

[14] These tests include: (1) size exclusion chromatography test for molecular weight distribution; (2) Coomassie Brilliant Blue (CBB) test; (3) Edman degradation profile; (4) peptide mapping profile; (5) fluorescent dye binding Test; (6) enzyme-linked immunosorbent assay (ELISA) tests; (7) Western blot test; (8) cytokine profiling; (9) acid digestion; (10) experimental autoimmune encephalomyelitis (EAE) blocking test; and (11) potency test (Petition at 11-13).

is responsible for its therapeutic activity, and that no single fraction and no one sequence of protein-like polypeptides is responsible for Copaxone's clinical efficacy (Petition at 13).

You also assert that other purported generic versions of glatiramer acetate have failed multiple chemical, biological, and immunological tests used to assure the consistency of Teva's manufacturing process and Copaxone's bulk properties, conclusively demonstrating that these products are not even similar (much less identical) to Copaxone's glatiramer acetate at the molecular level (Petition at 22). You assert that these studies confirm the need for a multidimensional drug evaluation program that includes chemical, biological, immunological, and toxicological tests for new glatiramoid products, by underscoring that superficial chemical similarities between glatiramoids do not guarantee that the products will produce identical biological or immunological effects and vice versa (Petition at 22).

You thus assert that until the chemical composition of Copaxone's glatiramer acetate has been fully characterized, or unless enough is learned about the features of Copaxone to both identify which of its features generate its therapeutic effects and rule out the possibility that variances undermine the drug's proven clinical safety and efficacy profile, FDA cannot approve an ANDA referencing Copaxone as the RLD because sameness cannot be demonstrated (Petition at 23). You assert that following settled Agency precedent, an ANDA applicant would need to take each potentially active component of glatiramer acetate and compare its effects — both alone and in combination with the other components — to the entire product in order to demonstrate that the candidate components achieve all the therapeutic effects of the product.

C. Studies on Glatiramoids Similar to Copaxone Show Significant Biological and Immunological Differences

You assert that even if an ANDA applicant could demonstrate similarities between a proposed ANDA product and Copaxone, past experience with glatiramer acetate variants strongly suggests that a follow-on product would present significant structural variations that produce distinct biological and immunological effects (Petition at 24). You assert that to date, Teva has evaluated several glatiramoids that are similar in certain respects to - but not the same as — the glatiramer acetate in Copaxone, and that these molecules differ both in their bulk properties and their biological and immunogenic effects[15] (Petition at 24-25). You also assert that tests conducted on several batches of a glatiramoid product called "Glatimer" marketed by Natco

[15] Specifically, you state that: (1) all products had substantially different Edman degradation profiles from that of glatiramer acetate, indicating substantial differences in their N-terminal sequences; (2) all products failed molecular weight distribution and chromatographic profile tests that are consistently achieved with Copaxone; (3) four out of five tested products failed at least one of the ELISA tests, indicating different biological and immunological activities from those of Copaxone; (4) three out of five tested products failed the relative potency specification for glatiramer acetate; and (5) one product was found to be highly toxic (Petition at 24-25).

Pharmaceuticals (Natco) outside the United States showed that Glatimer differed from Copaxone in at least 4 out of 8 parameters,[16] and also displayed poor batch-to-batch reproducibility.[17] You assert that these results indicate that Glatimer differs from Copaxone not only in amino acid sequence and structure, but also in biological activity profile (Petition at 35). You assert that the different immunological and biological profiles observed with Glatimer are directly related to differences from Copaxone in both the primary and secondary structures of Glatimer (Petition at 35-36). Moreover, you assert that significant differences in the immunomodulating activity of Glatimer may have serious implications for its safety, efficacy, and immunogenicity (Petition at 35). You thus assert that multiple analytical methods (chemical, biological, and immunological) should be used to compare any purported follow-on product to Copaxone (Petition at 35), and that a full preclinical and clinical testing program should be employed to evaluate the safety, effectiveness, and immunogenic potential of any purported generic version of Copaxone (Petition at 36).

D. Lack of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Correlations To Demonstrate Efficacy

You assert that because Copaxone has some local modes of action, and because there are no pharmacodynamic (PD) markers known to reflect the immunomodulatory and neuroprotective effects of the drug, there are no pharmacokinetic (PK) or PK/PD correlations between glatiramer acetate levels in plasma and drug efficacy (Petition at 17). You also assert that because there are no established PD markers for RRMS, a full clinical trial with clinically meaningful endpoints would likely be required to demonstrate drug efficacy and safety in patients — making this complex product particularly unsuitable for an ANDA product (Petition at 22).

E. Inability of Generics to Demonstrate "Sameness" of Active Ingredient

You state that when the chemical identity of the active ingredient in large or structurally complex molecules like proteins and protein-like polypeptides has not been, or cannot be fully characterized, FDA does not categorically prohibit the approval of such products through the ANDA pathway. Instead, we require the following to permit a finding of sameness: some "substantial certainty" about the composition to determine whether the two products' active ingredients share the core features responsible for producing the RLD's proven therapeutic effects; adequate information about those features of the active ingredient responsible for the drug's clinical efficacy and safety profile; and a clear understanding of the RLD's mechanism of

[16] Specifically, you state that peptide mapping and fluorescent dye binding tests demonstrate that the peptide sequences in, and the higher-order structure of Glatimer are different from those of the glatiramer acetate in Copaxone (Petition at 27-29); Western blot analysis shows that the amino acid sequences in Glatimer differ significantly from those in Copaxone (Petition at 30); the substantially different Edman degradation profiles of Copaxone and Glatimer indicate substantial differences in their N-terminal sequences (Petition at 27-28); Glatimer, unlike Copaxone, shows evidence of amino acid oxidation and the presence of di-tyrosine dimmers (Petition at 33); and microflow imaging techniques show that Glatimer tends to aggregate as large, needle-shaped particles that are polypeptidic in nature, whereas Copaxone shows only a small number of round-shaped particles (Petition at 33).

[17] Specifically, you cite batch-to-batch differences in molecular weight distribution as measured by size exclusion chromatography (Petition at 26-27); Coomassie Brilliant Blue test results (Petition at 27); ELISA and Western Blot profiles (Petition at 30); and cytokine-secretion profiles (Petition at 32).

action and knowledge gained from past clinical experience to rule out the possibility that any residual differences between the ANDA product and the RLD are clinically relevant (Petition at 18-19). You cite prior Agency decisions to support your assertions. For instance, you assert that FDA found sameness between a proposed generic menotropin and the RLD Pergonal despite the presence of differences between Pergonal and the ANDA product because the basic molecular structure of the RLD was well-characterized, [18] the proposed generic and the RLD were equally potent, the two products exhibited the same degree of batch-to-batch uniformity as measured by the same bioassays and specifications, and head-to-head clinical trials between Pergonal and another drug that exhibited the same kinds of microheterogeneity as the proposed ANDA product demonstrated no differences in safety and efficacy (Petition at 19). In contrast, you cite FDA's refusal to approve ANDAs for a generic version of Premarin (conjugated estrogens) because the Agency determined that Premarin's active moieties were neither definitively identified nor sufficiently well defined to permit an ANDA applicant to establish sameness of active ingredients[19] (Petition at 20). You also assert that with respect to other complex, incompletely characterized products such as pancreatic enzyme products and hyaluronidases, the agency has determined that existing chemical and bioanalytical tools are unlikely to demonstrate sameness (Petition at 20).

III. DISCUSSION

Based on your assertions and arguments, you request that the FDA not approve any ANDA for a generic version of Copaxone unless and until: (1) the glatiramer acetate in Copaxone has been fully characterized (i.e., every polypeptide sequence of the drug has been identified and quantified, and its structure fully elucidated) and an ANDA applicant has met the burden of proving that its product contains exactly the same polypeptide sequences, in the same amounts and with the same structures, as the fully characterized glatiramer acetate in Copaxone; or (2) all polypeptide sequences that contribute to the therapeutic effects of Copaxone's glatiramer acetate have been identified, the ANDA applicant has met the burden of proving that its product contains exactly the same clinically relevant polypeptide sequences, in the same amounts and with the same structures, as Copaxone's glatiramer acetate, and the ANDA applicant further has proven that any differences between the non clinically active polypeptides in its product and those in Copaxone's glatiramer acetate do not undermine the clinically active polypeptides' safety, efficacy, toxicology, and immunology profiles.

As FDA's regulations and preamble reflect, and as the court in *Serono* ruled, we have broad discretion in determining whether an ANDA applicant has submitted sufficient information upon which we can reasonably conclude that the generic drug product's active ingredient is the "same as" that of the RLD. A finding of sameness does not, however, necessitate a finding of

---

[18] Naturally occurring variations ("microheterogeneity") were found to exist between the products' carbohydrate side chains. However, the ANDA applicant (Ferring) had shown that both the protein backbones and specific amino acid sequences in the two products were identical.

[19] FDA explained that because the features of the drug that made "clinically meaningful contributions to the drug's therapeutic effects" were at that time unknown, no ANDA product could be approved until such features had been "sufficiently defined," which would in turn require the proposed generic applicant to provide information sufficient to identify and characterize those constituents of the product that are responsible for the drug's therapeutic effects.

"complete chemical identity." Thus, the Agency may consider other criteria to determine sameness, taking into account the complexity of the active ingredient. Any such determination would be highly specific to the active ingredient.[20] For instance, given the complexity of Copaxone, we may require that any ANDA sponsor demonstrate active ingredient sameness through a multi-criteria test or series of tests, each criterion of which captures different aspects of the active ingredient's "sameness," and which together would provide overlapping evidence by which an ANDA applicant could demonstrate active ingredient sameness within the meaning of the Act and FDA regulations. Although we cannot state with any certainty what these criteria may be (as any such determination is likely to would be informed by our review of the ANDA before us) we may require an ANDA sponsor to show, among other things, equivalence to the physicochemical properties of Copaxone, and/or equivalence of structural signatures for Copaxone's polymerization chemistry,[21] and/or equivalence in biochemical/biological assays.

Your arguments that certain other glatiramer acetate products do not have the same biological and immunological properties as Copaxone are unpersuasive. The products you identified were not approved by FDA under an ANDA, and thus do not purport to have met the approval requirements established by statute and FDA regulations. The existence of glatiramer products which you assert do not have the same active ingredient as Copaxone does not preclude the possibility that a generic version of glatiramer acetate might be able to meet rigorous standards for demonstrating sameness of active ingredient to Copaxone.

We are aware that any criteria for establishing "sameness" in the context of glatiramer acetate would have to take into account the inherent complexity of this active ingredient; however, we deny the specific requests in your Petition regarding the approvability of any glatiramer acetate injection ANDA because it would be premature and inappropriate to definitively opine on this matter at this time. Such an action could, in effect, render a decision on a specific aspect of an

---

[20] Your descriptions of FDA's consideration of ANDAs for Premarin and menotropins (Pergonal) support the Agency's view that any finding of active ingredient sameness must be based on relevant scientific information specific to each active ingredient. Neither the Premarin nor menotropins example is directly on point for the Agency's consideration of glatiramer acetate. For example, although Premarin, menotropins, and glatiramer acetate are all mixtures of molecular entities, these products are composed of entirely different molecular entities having vastly different molecular structures. Premarin is a naturally sourced product and the proposed generic products were synthetically manufactured. For Premarin, we determined that we could not make a finding of active ingredient sameness for synthetic versions of Premarin because the Premarin active ingredient had not been adequately characterized. For Pergonal, which involved a naturally sourced RLD and generic drug, we expected the active ingredient in the generic version to have the same primary structure (assured by using the same natural source material), potency, and degree of batch-to-batch uniformity as the innovator's active ingredient. We concluded that any differences between the generic drug product's active ingredient and Pergonal's active ingredient were not clinically significant. Glatiramer acetate, in contrast, is synthetically manufactured and has its own complex, heterogeneous molecular structure. It is reasonable and appropriate for the Agency to take into account the differences among these drugs, and to establish approaches to the approval of ANDAs that are specific to each active ingredient.

[21] Polymerization is a process in which relatively small molecules (called monomers) combine chemically to produce a larger, chain-like molecule (called a polymer). The monomer molecules may all be alike, or they may represent two, three, or more different compounds. Generally, polymerization consists of sequential steps including initiation, propagation and termination. In comparison, depolymerization refers to a process that breaks down the polymers into smaller fragments containing a fewer number of monomers.

ANDA before the Agency has had an opportunity either to fully consider specific data and information in such an application or to provide the procedural rights that accompany FDA actions on applications.[22] Were we, for example, to grant your requests to impose certain specific requirements for glatiramer acetate injection applications, we could, in effect, be taking final action on the approvability of specific aspects of an application for a glatiramer acetate injection drug product before we have had an opportunity to fully review data and information submitted by an applicant or to provide such applicant with appropriate procedural protections.

As described in section I.B of this response, section 505(q)(1)(F) of the Act requires FDA to take final Agency action on the Petition within 180 days of submission. Therefore, we must take action on the Petition at this time. However, FDA has made no final determination with respect to whether to approve or not approve any ANDA for a glatiramer acetate injection drug product.

The Act and FDA regulations establish procedural protections for applicants in the context of application review. Section 505 of the Act and FDA's regulations at 21 CFR part 314 describe certain procedures by which the Agency reviews an NDA or ANDA and notifies an applicant if it determines that an application is approved (21 CFR 314.105) or may not be approved (section 505(c) and 505(j) of the Act, 21 CFR 314.125 and 314.127), or identifies the deficiencies in the application and the steps an applicant may take to respond to the deficiencies (21 CFR 314.110). In addition, the statute and regulations describe a specific process through which an applicant whose application the Agency has found does not meet the requirements for approval may challenge the Agency's determination (section 505(c)(1)(B) and (d) of the Act; 21 CFR 314.200). Under this process, the Agency will give the applicant notice of an opportunity for a hearing on whether the application is approvable, with a specific time frame and process, should the applicant request such a hearing (Id.). These procedures ensure that applicants have an adequate opportunity to challenge a finding by the Agency that a product does not meet the requirements for approval.

There is no evidence that in enacting section 505(q) of the Act, Congress intended to short-circuit the application review process or to vitiate an ANDA or NDA applicant's procedural rights by requiring that the Agency make decisions on complex scientific issues specific to pending applications (e.g., whether sameness of an active ingredient can be demonstrated) on a piecemeal basis.[23] We do not interpret section 505(q) to require that the Agency render a final

---

[22] We also note that under applicable statutory and regulatory provisions, we are generally prohibited from disclosing any determinations regarding the filing or approvability of any particular NDA or ANDA for a glatiramer acetate injection drug product before we have reached a final decision on whether to approve or not approve the application.

[23] In other citizen petition responses, we have responded to requests related to general standards for approval (e.g., bioequivalence criteria for generic drug products or the appropriateness of omitting certain information protected by patent from a proposed drug product's labeling) that may pertain to one or more pending drug applications without commenting on the approvability of any particular aspect of a specific pending application. We believe that this approach of describing our general policies or standards for approval of a drug application would not be appropriate in this case because, as stated, our review of a given ANDA or NDA would be expected to inform our decisions regarding the sufficiency of the specific data and information needed to demonstrate the sameness of a particular active ingredient. We will continue to evaluate each citizen petition on a case-by-case basis with respect to the appropriateness of responding to the citizen petition's requests vis-à-vis any pending applications.

Agency decision within 180 days on specific requirements for approval of any ANDA for a glatiramer acetate injection drug product when a decision on the approvability of any such application has not yet been made. We therefore are denying your requests without comment on the specific requirements for approval of any ANDA for a glatiramer acetate injection drug product.

Although we are denying your request that the Agency take specific actions with respect to ANDAs for glatiramer acetate injection at this time, FDA is actively considering what evidence would be sufficient to show that the active ingredient in a proposed product is the same as that in Copaxone. The information you have provided in your Petition regarding the complexity of these drug products and the scientific challenges they pose will inform FDA's assessment of the types of information needed to support generic glatiramer acetate injection products.

IV. CONCLUSION

For the reasons described in this response, the Petition is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research